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EXAMINER	
NIEBAUER, RONALD T	

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1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,405	NATHAN ET AL.	
	Examiner	Art Unit	
	RONALD T. NIEBAUER	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments and arguments filed 3/14/08 and affidavit filed 12/29/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Election/Restrictions

The original restriction requirement was mailed 9/26/06. Applicants replied on 1/25/07. Since the response was not fully responsive another reply dated 6/19/07 was made by the applicant. In response to the first office action applicants have cancelled claims 2,5-14, amended claims 1,3-4 and added new claims 15-17 (3/14/08). Applicant's election of Group I (claim 2 drawn to in vivo treatment of cell necrosis) and the species of elastase inhibitor III (MeOSuc-Ala-Ala-Pro-Val-CMK) for the elastase inhibitor; the regulation of expression by pro- and anti-apoptotic proteins for the inhibitor of apoptosis; neuronal cells as the cell type; dementia as the disease type in the reply filed on 6/19/07 is acknowledged. Applicant have amended claim 3 to recite 'administration of an anti-apoptotic agent'. However, there has not been an election of a species of anti-apoptotic agent. It is noted that applicant previously identified the regulation of expression by pro- and anti-apoptotic proteins for the inhibitor of apoptosis. However, the claims examined were unclear (see 9/7/07 page 4) and the wherein clause regarding apoptosis was not interpreted as limiting the claim (see 9/7/07 page 8). However, as instantly claimed, an anti-apoptotic agent is an element of claim 3. Applicants previous identification of the regulation of expression by pro- and anti-apoptotic proteins for the inhibitor of apoptosis is not an election of

an anti-apoptotic agent since the actual agent is unclear. Applicants (page 2 last paragraph of 6/19/07) refer to a methodology of regulation and refer to a Li reference. However, it is unclear how regulation is an agent. Further, the Li reference could not be found. In particular the Li reference is apparently from Acta. Anaesthesiol Sin. However, the reference is unclear because the full title and journal article title have not been provided. Using the provided information no such reference could be located. As such, 'regulation' as by Li et al. is not an adequate species of anti-apoptotic agent. Therefore, the most recent restriction requirement was to identify (or clarify) a species of anti-apoptotic agent.

The previous election of elastase inhibitor III (MeOSuc-Ala-Ala-Pro-Val-CMK) for the elastase inhibitor and dementia as the disease type remains of record.

Applicant's election without traverse of the anti-apoptotic agent as z-VAD-fluoromethylketone in the reply filed on 12/29/08 is acknowledged.

Applicants note that the elected species is not specifically recited in the specification and applicants have submitted a declaration in which they conclude that data supports reduction of cell necrosis and that one of ordinary skill in the art would recognize z-VAD-fluoromethylketone as a member of caspase inhibitors.

Since the elected species of z-VAD-fluoromethylketone is not recited in the claims, whether or not the species represents new matter is not addressed at this stage of examination. Applicants arguments with regards to reduction of cell necrosis are addressed below in the 112 section.

As discussed below, the elected species have been found in the prior art and all claims have been rejected either under 102 or 103. Any art that was uncovered in the course of searching for the elected species is also cited herein.

Claims 15-17 are new claims which read on the elected species.

Claims 2,5-14 have been cancelled.

Claims 1,3-4,15-17 are under consideration.

Claim Rejections - 35 USC § 112

Claims were previously rejected under 112 first paragraph. Since the claims have been amended and new claims have been added an updated rejection appears below based on the instant claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cell necrosis or a neurodegenerative disorder associated therewith, does not reasonably provide enablement for prevention of cell necrosis or a neurodegenerative disorder associated therewith. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not

precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

Claims 15-17 are drawn to a method of treating and/or preventing cell necrosis or a neurodegenerative disorder associated therewith. Applicants have elected dementia as the disease type. It is noted that dementia is associated with numerous neurodegenerative disorders including Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and Creutzfeldt-Jakob disease for example. It is noted that the specification (page 7) teach that necrosis encompasses intermediate cell necrosis states.

Please note that the term "prevent" means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be prevented with current therapies (other than certain vaccination regimes) – including preventing such disorders as Alzheimer's disease, which is clearly not recognized in the medical art as being a preventable condition.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the art in preventing Alzheimers (a type of dementia) is highly unpredictable.

As stated by Hingley (FDA document page 2):

"While researchers now have a deeper understanding of the brain and behavioral changes characterizing the disease, Alzheimer's remains shrouded in mystery. Its cause is still unknown…."
And (page 4)
"..no cure for Alzheimer's is available now…"

Hingley further sates that developing treatment and prevention is an ongoing challenge (page 2). Hingley states that the most used drug for Alzheimers treatment does not stop or slow the disease's progression (page 2). As such, one would recognize that the prevention of Alzheimers is highly unpredictable.

Further, Solomon (Expert Opin. Investig. Drugs 2007) discusses recent approaches for the treatment of Alzheimers (page 819). Solomon teach that (page 819) an increased knowledge of the pathophysiology of the disease and development of treatments and interventions are required for prevention of the disease (page 819).

It is noted that Solomon is dated 2007 and is post filing date art (the instant application is a 371 of PCT/IL03/00253 3/26/03 and claims foreign priority back to 3/26/02). As such, Solomon is numerous years after the filing date. However, even after numerous years from the filing date of the instant application Solomon teach that (page 819) 'Prevention of Alzheimer's disease requires the development of safe treatments or interventions that could be used in a large number of elderly people at risk, many of whom might never have the disorder. The development of such approaches depends on increased knowledge of the pathophysiology of the disease'. As such, one would recognize that prevention of Alzheimers disease is highly unpredictable.

Solomon teach that mouse models have been used to study Alzheimers disease and that the models have been essential for progress in the field (page 820-821 section 4). Solomon state that it will 'take considerable effort to determine whether such approaches will work in humans' (page 826).

Taken together the state of the art teach that preventing Alzheimers is highly unpredictable.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

Examples (such as example 1) are provided in which model systems were used in vitro and cell death was monitored. However, the specification does not provide a correlation between the ability to treat a non-diseased population in vitro and the ability to prevent any and all neurodegenerative disorders. The specification states that Figure 5 reveals prevention of KCN-induced necrosis (page 16). However, figure 5 shows that 31% of the KCN-induced cells treated with an elastase inhibitor are necrotic. One would not associate 31% of cells being necrotic with prevention of necrosis. One would not associate 31% of cells being necrotic to the prevention of any and all neurodegenerative disorders. One would not recognize KCN-induced cells as representative of complex disease states such as dementia.

(8) The quantity of experimentation necessary:

Experimentation is required in numerous areas particularly related to how to use the method and determination if it would be a useful method for prevention of diseases. It is also

unknown how much of an effect, if any, the method would have in prevention of disease states especially complex and unpredictable disease states such as Alzheimers. Considering the state of the art as discussed by the references above, particularly with regards to the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Response to Arguments 112 enablement

Claims were previously rejected under 112 first paragraph. Since the claims have been amended and new claims have been added an updated rejection appears above based on the instant claims. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that the art recognize that neurodegenerative disorders are caused by a final common pathway of neurotoxicity.

Applicants argue that the cited references are irrelevant to the present invention.

Applicants argue that Hingley does not reflect the level of knowledge in the art.

Applicants argue that the prevention is directed towards preventing downstream events.

Applicants argue that Francis support prevention.

Applicants argue that a report is provided that illustrate positive effects of the use of elastase inhibitors.

In an affidavit filed 12/29/08 Applicants argue that experimentation has been undertaken in which elastase inhibitors and z-VAD-fmk have been used as summarized in Figures 1 and 2. Applicants conclude that the data supports significant effect in the prevention of necrosis.

Applicants argue that one of ordinary skill in the art would recognize z-VAD-fluoromethylketone as a member of caspase inhibitors.

Applicant's arguments filed 3/14/08 and affidavit filed 12/29/08 have been fully considered but they are not persuasive.

Although Applicants argue that the art recognize that neurodegenerative disorders are caused by a final common pathway of neurotoxicity, it is noted that the reference states that the neurotoxicity is 'thought to contribute' (see page 8 of applicants reply). A thought about what may contribute to a disease would not lead one to say that such disease can necessarily be prevented. Further, neurotoxicity is not the equivalent of necrosis as is instantly claimed. Further, Hingley and Solomon as discussed above teach the unpredictability in the art.

Although Applicants argue that the cited references are irrelevant to the present invention, as cited above one of the Wands factors is the state of the prior art and another is the predictability or unpredictability of the art. The instantly rejected claims are drawn to methods of preventing neurodegenerative disorders associated with cell necrosis. Applicants have elected dementia as the patient population. Alzheimers disease is a form of dementia. As such, Hingley and Solomon which deal with unpredictability in preventing Alzheimers are relevant prior art.

Although Applicants argue that Hingley does not reflect the level of knowledge in the art, it is noted that the Hingley article is a correspondence from the US Food and Drug Administration, a reputable source. Hingley had to be knowledgeable about the art to assimilate and present the information presented in the article. Further, several of the quotes used in the article are from Steven T. DeKosky, M.D. the director of the Alzheimers Disease Research

Center at the University of Pittsburgh (page 1). As such, one would recognize the article as being reputable and reflective of the knowledge in the art.

Although Applicants argue that the prevention is directed towards preventing downstream events, the instant claims do not use the words 'downstream events'. The instant claims are drawn to methods of preventing neurodegenerative disorders associated with cell necrosis which as discussed above is highly unpredictable.

Although Applicants argue that Francis support prevention, Francis expressly state that the exact cause of neurodegeneration is uncertain (see page 10 of applicants reply). Although Francis conclude that AD and VaD have considerable overlap in pathways that mediate cell death, one would not be led to conclude that a mere overlap in pathways that mediate cell death is necessary and sufficient to say that any and all neurodegenerative disorders can be prevented.

Although Applicants argue that a report is provided that illustrate positive effects of the use of elastase inhibitors, section 2164.05 of the MPEP states that applicant may submit factual affidavits to show what one skilled in the art new at the time of filing and that the weight given to a declaration or affidavit will depend on the amount of factual evidence. In the instant case, the report is not a declaration or affidavit. Further, one would not conclude that 'positive effects of the use of elastase inhibitors' is the equivalent of preventing any and all neurodegenerative disorders associated with cell necrosis.

With respect to the declaration filed 12/29/08 although Applicants conclude that the data supports significant effect in the prevention of necrosis, an effect in the prevention of necrosis is not equivalent to the prevention of cell necrosis or a neurodegenerative disorder associated

therewith. Section 2164.05 of the MPEP states that the burden falls on the applicant to provide persuasive arguments and that any showings must be commensurate with the scope of the claimed invention. In the instant case, one would not recognize U-937 cells as representative of any and all neurodegenerative disorder associated with cell necrosis. Further applicants expressly state that 'both inhibitors were not able to protect the cells from KCN induced cell death by themselves'. Claim 15 is drawn to a method using an elastase inhibitor. As such, applicants statement ('both inhibitors were not able to protect the cells from KCN induced cell death by themselves') is evidence that claim 15 which is only drawn to the use of an elastase inhibitor is not sufficient to protect the cells from KCN induced cell death. Further, Figure 1 shows approximately 50% cell survival at 10mM KCN with z-VAD-fmk and elastase inhibitor III. One would not recognize 50% cell survival as prevention of cell necrosis or a neurodegenerative disorder associated therewith. Figure 2 shows approximately 30% necrotic cells at 10mM KCN with z-VAD-fmk and elastase inhibitor III. One would not recognize 30% necrotic cells as prevention of cell necrosis or a neurodegenerative disorder associated therewith. Further, it is noted that none of the instant claims recite z-VAD-fmk which based on applicants assertions is a critical element.

Although Applicants argue that one of ordinary skill in the art would recognize z-VAD-fluoromethylketone as a member of caspase inhibitors, such argument does not deal with whether or not the specification reasonably provides enablement for prevention of cell necrosis or a neurodegenerative disorder associated therewith.

For the reasons set forth herein, the declaration under 37 CFR 1.132 filed 12/29/08 is insufficient to overcome the instant rejections.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims were previously rejected based on Gyorkos et al (US 6,001,813). Since the claims have been amended and new claims have been added a new rejection appears below.

Claims 1,4,15,17 are rejected under 35 U.S.C. 102(b) as being anticipated by Gyorkos et al (US 6,001,813).

Gyorkos et al. teach a method of administering an elastase inhibitor to a host in need thereof (claim 10-11). Gyorkos teach that the inhibitors are useful for the treatment of conditions including Alzheimer's disease (abstract and column 1 line 55) which is a form of dementia which meets the patient population of the instant claims. Gyorkos teach the use of an effective amount of the inhibitor (claim 10) as recited in instant claims 1,15. Gyorkos teach that the diseases are human diseases (column 1 line 42) and teach human treatment (column 3 line 10). Since humans have neuronal cells the limitations as recited in claims 4,17 are met.

It is noted that claims 1 and 15 state that an intracellular elastase enzyme is inhibited. Gyorkos teach the inhibition of serine proteases (claim 10) specifically human neutrophil elastase (claim 12). Gyorkos teach that human neutrophil elastase is secreted by cells in response

to certain stimuli (column 1 line 23-26). Since human neutrophil elastase is secreted by cells it must be present inside cells in order to be secreted thus meeting the claimed limitations. It is noted that the claims recite that the elastase inhibitor is capable of entering cells. Gyorkos teach a variety of compositions for various administrations of the inhibitor (column 5 line 25-column 6 line 36). Further it is noted that Gyorkos expressly teach that the inhibitors are elastase inhibitors (claim 12) thus there is a reasonable basis, absence evidence to the contrary, that the inhibitors of Gyorkos are capable of entering cells.

It is noted that 'necrosis' is defined on page 7 of the specification.

It is noted that claims 15,17 are drawn to a methods of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administrations.

Response to Arguments 102 Gyorkos

Claims were previously rejected based on Gyorkos et al (US 6,001,813). Since the claims have been amended and new claims have been added a new rejection appears above. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that Gyorkos is drawn to extracellular proteolytic activity.

Applicants assert that Gyorkos is not an enabling reference.

Applicants argue that Gyorkos is not similar to the methods claimed.

Applicants argue that the mechanism of Gyorkos is different.

Applicant's arguments filed 3/14/08 have been fully considered but they are not persuasive.

Although Applicants argue that Gyorkos is drawn to extracellular proteolytic activity, Gyorkos teach the inhibition of serine proteases (claim 10) specifically human neutrophil elastase (claim 12). Gyorkos teach that human neutrophil elastase is secreted by cells in response to certain stimuli (column 1 line 23-26). Since human neutrophil elastase is secreted by cells it must be present inside cells in order to be secreted thus meeting the claimed limitations. Gyorkos teach the active steps of the instant claims.

Although Applicants assert that Gyorkos is not an enabling reference, section 2121 of the MPEP states that prior art is presumed to be enabling and the burden is on the applicant to provide facts rebutting the presumption of operability.

Although Applicants argue that Gyorkos is not similar to the methods claimed, the active step of the instant claims is administration of an elastase inhibitor which is taught by Gyorkos. Further, Gyorkos teach those with Alzheimers as a patient population.

Although Applicants argue that the mechanism of Gyorkos is different, it is noted that the instant claims are drawn to methods involving an administration step, not a mechanism. Gyorkos teach human treatment (column 3 line 10). Since humans have neuronal cells the limitations as recited in claims 4,17 are met.

Claims were previously rejected based on Miyano et al (US 4,683,241). Since the claims have been amended and new claims have been added and a new IDS submitted new rejections appear below.

Claims 15,17 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyano et al (US 4,683,241).

Miyano et al. teach a method of administering an elastase inhibitor to a host in need thereof (claim 1) for the management of alleviation of elastase mediated diseases such as arthritis (column 1). Miyano teach the use of an effective amount of the inhibitor (claim 1) as recited in instant claims 15. Miyano teach uses in mammals (claim 1) and specifically refer to human leukocyte elastase (example 42). Since humans have neuronal cells the limitations as recited in claim 17 are met.

It is noted that claim 15 states that an intracellular elastase enzyme is inhibited. Miyano specifically refer to human leukocyte elastase (example 42). It is noted that the claims recite that the elastase inhibitor is capable of entering cells. Miyano teach a variety of compositions for various administrations of the inhibitor (column 10). Further it is noted that Miyano expressly teach that the inhibitors are elastase inhibitors (claim 1) thus there is a reasonable basis, absence evidence to the contrary, that the inhibitors of Miyano are capable of entering cells.

It is noted that 'necrosis' is defined on page 7 of the specification.

It is noted that claims 15,17 are drawn to a methods of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administrations.

Claims 1,4,15,17 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyano et al (US 4,683,241) as evidenced by Proskuryakov et al (Experimental Cell Research 283(2003) pages 1-16 as cited in IDS 3/14/08).

Miyano et al. teach a method of administering an elastase inhibitor to a host in need thereof (claim 1) for the management of alleviation of elastase mediated diseases such as arthritis (column 1), specifically rheumatoid arthritis.

Proskuryakov (Table 1) teach that inflammatory diseases are associated with cell necrosis. Since Miyano teach inflammatory diseases such as rheumatoid arthritis the patient population of claim 1 is met since such diseases are associated with cell necrosis. Proskuryakov is cited as a universal fact (see MPEP 2124) to show that the patient population of Miyano meet the limitations of the instant claims.

Miyano teach the use of an effective amount of the inhibitor (claim 1) as recited in instant claims 1,15. Miyano teach uses in mammals (claim 1) and specifically refer to human leukocyte elastase (example 42). Since humans have neuronal cells the limitations as recited in claims 4,17 are met.

It is noted that claims 1,15 state that an intracellular elastase enzyme is inhibited. Miyano specifically refer to human leukocyte elastase (example 42). It is noted that the claims recite that the elastase inhibitor is capable of entering cells. Miyano teach a variety of compositions for various administrations of the inhibitor (column10). Further it is noted that Miyano expressly teach that the inhibitors are elastase inhibitors (claim 1) thus there is a reasonable basis, absence evidence to the contrary, that the inhibitors of Miyano are capable of entering cells.

It is noted that 'necrosis' is defined on page 7 of the specification.

It is noted that claims 15,17 are drawn to a methods of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administrations.

Response to Arguments 102 Miyano

Claims were previously rejected based on Miyano et al (US 4,683,241). Since the claims have been amended and new claims have been added and a new IDS submitted new rejections appear above. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that methods of treating arthritis are unrelated to the instant invention.

Applicant's arguments filed 3/14/08 have been fully considered but they are not persuasive.

Although Applicants argue that methods of treating arthritis are unrelated to the instant invention, it is noted that claims 15,17 are drawn to methods of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administrations. Further, claim 1 reads on methods of treating cell necrosis and does not exclude those with arthritis. In fact, original claim 5 of the instant application states that rheumatoid arthritis is a disease associated with cell necrosis. As such, the patients with rheumatoid arthritis as taught by Miyano are related to the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims were previously rejected based on Gyorkos et al. (US 6,001,813), and Stein et al. (Biochemistry 1986 v25 5414-5419). Since the claims have been amended and new claims have been added a new rejection appears below.

Claims 1,4,15,17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gyorkos et al. (US 6,001,813), and Stein et al. (Biochemistry 1986 v25 5414-5419).

As discussed above, Gyorkos et al. teach a method of administering an elastase inhibitor to a host in need thereof (claim 10-11). Gyorkos teach that the inhibitors are useful for the treatment of conditions including Alzheimer's disease (abstract and column 1 line 55) which is a form of dementia. Gyorkos teach the use of an effective amount of the inhibitor (claim 10) as recited in instant claims 1,15. Gyorkos teach that the diseases are human diseases (column 1 line 42) and teach human treatment (column 3 line 10). Humans have neuronal cells as recited in claims 4,17.

Gyorkos does not expressly teach the elected elastase inhibitor, elastase inhibitor III. Gyorkos teach tripeptides as inhibitors (claim 1 and abstract).

Stein also teach elastase inhibitors (abstract). Stein specifically teach a chloromethyl ketone peptide (MeOSuc-Ala-Ala-Pro-Val-CH2Cl) as an elastase inhibitor (abstract) which is the elected species of the current invention. Stein teach that the peptide derived chloromethyl ketons are irreversible inhibitors (age 5414 first paragraph). One of skill in the art would have been motivated to substitute the chloromethyl ketone peptide disclosed by Stein for the tripeptide disclosed by Gyorkos because both are known elastase inhibitors and Stein teach that the peptide derived chloromethyl ketones have desired qualities such as being irreversible inhibitors of serine proteases (elastase is a serine protease). As such one would be motivated to treat the patient population of Gyorkos (those with Alzheimers) using the peptide of Stein. One would have had a reasonable expectation for success since the peptides used are known elastase inhibitors. The claims would have been obvious because the substitution of one known element (chloromethyl ketone elastase inhibitor (MeOSuc-Ala-Ala-Pro-Val-CH2Cl) of Stein) for another (tripeptides of Gyorkos) would have yielded predictable results to one or ordinary skill in the art at the time of the invention.

It is noted that claims 1 and 15 state that an intracellular elastase enzyme is inhibited. It is noted that the claims recite that the elastase inhibitor is capable of entering cells. Since Stein teach the elected species of elastase inhibitor such inhibitor would have the claimed properties as recited in the instant claims.

It is noted that 'necrosis' is defined on page 7 of the specification.

It is noted that claims 15,17 are drawn to a methods of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administrations.

Response to Arguments 103 Gyorkos and Stein

Claims were previously rejected based on Gyorkos et al (US 6,001,813) and Stein et al. (Biochemistry 1986 v25 5414-5419). Since the claims have been amended and new claims have been added a new rejection appears above. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that Gyorkos is not similar to the methods claimed.

Applicants argue that the mechanism of Gyorkos is different.

Applicant's arguments filed 3/14/08 have been fully considered but they are not persuasive.

Although Applicants argue that Gyorkos is not similar to the methods claimed, the active step of the instant claims is administration of an elastase inhibitor which is taught by Gyorkos. Further, Gyorkos teach those with Alzheimers as a patient population.

Although Applicants argue that the mechanism of Gyorkos is different, it is noted that the instant claims are drawn to methods involving an administration step, not a mechanism. Gyorkos teach human treatment (column 3 line 10). Since humans have neuronal cells the limitations as recited in claims 4,17 are met.

This is a new rejection necessitated by applicants amendments and addition of new claims.

Claims 1,3-4,15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gyorkos et al. (US 6,001,813), and Rohn et al (American Journal of Pathology v158(2) Jan 2001 pages 189-198).

As discussed above, Gyorkos et al. teach a method of administering an elastase inhibitor to a host in need thereof (claim 10-11). Gyorkos teach that the inhibitors are useful for the treatment of conditions including Alzheimer's disease (abstract and column 1 line 55) which is a form of dementia. Gyorkos teach the use of an effective amount of the inhibitor (claim 10) as recited in instant claims 1,15. Gyorkos teach that the diseases are human diseases (column 1 line 42) and teach human treatment (column 3 line 10). Humans have neuronal cells as recited in claims 4,17.

Gyorkos does not expressly teach the further administration of an anti-apoptotic agent as recited in claims 3,16

Gyorkos teach that the inhibitors are useful for the treatment of conditions including Alzheimer's disease (abstract and column 1 line 55) which is a form of dementia.

Rohn also provide teachings regarding Alzheimers disease. Rohn teach that the results provide evidence that there is an association between neurofibrillary tangles (NFTs) and the activation of apoptotic pathways in Alzheimer's disease (abstract). Rohn teach that preventing caspase activation is one aspect of neurodegeneration amenable to therapeutic intervention (page 197 last paragraph). Rohn specifically teach the use of z-FAD-fmk (page 190 materials section) as a caspase inhibitor (page 192, Figure 1c). Rohn teach that treatment with caspase inhibitor z-FAD-fmk showed the involvement of caspases in the neurodegenerative process (page 193 first

complete paragraph). Since both Gyorkos and Rohn are drawn to therapeutic intervention of Alzheimers it naturally flows to combine the individual teachings of the prior art. In the instant case one would be motivated to administer to those with Alzheimers both the elastase inhibitor as taught by Gyorkos and the anti-apoptotic agent (specifically z-FAD-fmk, a caspase inhibitor) as taught by Rohn. One would have a reasonable expectation of success since both are taught to have beneficial effects against Alzheimers. In the instant case the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

It is noted that claims 1 and 15 state that an intracellular elastase enzyme is inhibited. Gyorkos teach the inhibition of serine proteases (claim 10) specifically human neutrophil elastase (claim 12). Gyorkos teach that human neutrophil elastase is secreted by cells in response to certain stimuli (column 1 line 23-26). Since human neutrophil elastase is secreted by cells it must be present inside cells in order to be secreted thus meeting the claimed limitations. It is noted that the claims recite that the elastase inhibitor is capable of entering cells. Gyorkos teach a variety of compositions for various administrations of the inhibitor (column 5 line 25-column 6 line 36). Further it is noted that Gyorkos expressly teach that the inhibitors are elastase inhibitors (claim 12) thus there is a reasonable basis, absence evidence to the contrary, that the inhibitors of Gyorkos are capable of entering cells.

It is noted that claims 3 and 16 state 'cause partial conversion of necrosis to apoptosis'. Since the prior art obviate the active steps (i.e. administration) using the claimed elements

(elastase inhibitor and anti-apoptotic agent) the claim limitations are met obvious evidence to the contrary.

Response to Arguments 103 Gyorkos and Rohn

This is a new rejection based on applicants amendments and addition of new claims. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that Gyorkos is not similar to the methods claimed.

Applicants argue that the mechanism of Gyorkos is different.

Applicant's arguments filed 3/14/08 have been fully considered but they are not persuasive.

Although Applicants argue that Gyorkos is not similar to the methods claimed, the active step of the instant claims is administration of an elastase inhibitor which is taught by Gyorkos. Further, Gyorkos teach those with Alzheimers as a patient population.

Although Applicants argue that the mechanism of Gyorkos is different, it is noted that the instant claims are drawn to methods involving an administration step not a mechanism. Gyorkos teach human treatment (column 3 line 10). Since humans have neuronal cells the limitations as recited in claims 4,17 are met.

Conclusion

In the instant case applicants have amended and added new claims. In particular it is noted that claim 3 has been amended to recite administration of an anti-apoptotic agent which necessitated a new search.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

In the instant case, one of the references submitted in the IDS dated 3/14/08 (which is after the date the first action was mailed (9/7/07)) is used in an instant rejection.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 3/14/09 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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